Is subclinical hypothyroidism a risk factor for myocardial infarction? A comparative study of a cohort of young Pakistani men

Subclinical hypothyroidism myocardial infarction

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Abstract

Aim: Myocardial infarction (MI) is a major cause of death globally with a rising incidence at a younger age. Subclinical hypothyroidism (SCH) is an asymptomatic condition with raised serum thyroid-stimulating hormone (TSH) and normal free thyroid hormones. SCH has been linked with MI previously, but local data are not available. The present study was done to determine the relation between SCH and MI in young men from the local population.

Material and Methods: The cross-sectional study compared male patients with MI (n=75) with age-matched controls (n=75) for the presence of subclinical hypothyroidism and other clinical risk factors including blood pressure, waist circumference and fasting blood glucose (FBG). For the assessment of SCH, serum thyroid hormone profile was done, including TSH, free tri-iodothyronine (fT3) and free thyroxine (fT4) levels.

Results: The incidence of SCH in MI patients and healthy control subjects were 12% and 5%, with the difference being statistically insignificant (p=0.15.). No differences were observed between the two groups in thyroid hormone profile and other clinical risk factors studied.

Discussion: SCH does not appear to be associated with an increased risk of MI in local population of Pakistani men. Considering the study limitations, larger prospective trials are warranted to inform robust outcomes.

Keywords

Thyroid hormones; Subclinical hypothyroidism; Myocardial infarction; Cardiovascular diseases

Introduction

Myocardial infarction (MI), a condition characterized by irreversible ischemic damage of the myocardium due to obstruction to coronary blood flow, is a major cause of death and compromised quality of life of survivors globally. Many modifiable and non-modifiable risk factors of MI have been recognized over the years, including family history, smoking, obesity, dyslipidemia and psychosocial disorders [1, 2]. Subclinical hypothyroidism (SCH) is an asymptomatic condition characterized by raised serum thyroid-stimulating hormone (TSH) levels and normal free thyroid hormones, including free triiodothyronine (fT3) and thyroxine (fT4). SCH and overt hypothyroidism share causes, which include iodine deficiency, autoimmune thyroiditis, surgical or ablative procedures induced, and certain medications [3]. SCH has been proposed as a risk factor for hypertension, hyperlipidemia and hyperhomocysteinemia, which are also associated with the pathophysiology of cardiovascular diseases [4-6]. Overt thyroid disease is a known cause of atherosclerotic cardiovascular abnormalities [7]. Subclinical thyroid dysfunction itself is linked with cardiac diseases due to the sensitivity of the cardiovascular system to thyroid hormones at the cellular and molecular levels [8]. Thyroid hormones influence cardiac myocytes via both genomic and non-genomic mechanisms and stimulate or suppress the transcription of specific target genes involved in the maintenance of cardiac integrity [9]. Nonetheless, adverse cardiovascular outcomes due to subclinical thyroid abnormalities remain contentious and unclear, and local data on this aspect are missing. Furthermore, the benefits of mild SCH treatment in the prevention of MI remain controversial. The present study was conducted to highlight any potential nexus between SCH and MI in the local population of Pakistan.

Material and Methods

The cross-sectional comparative study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. Adult male patients (n=75), between the ages of 18 to 55 years, admitted to Punjab Institute of Cardiology, Lahore, Pakistan following an acute MI (Group 1) were recruited through a non-random convenience sampling. There is growing evidence of increasing risk of MI in young males, hence a younger age group was included in the study [10]. Age-matched healthy males (n=75) without any history of MI were enrolled as controls (Group 2). A relatively young age group was chosen, as the incidence of MI is drastically increasing in young Pakistani men [11]. Subjects with a previously known medical history of diabetes mellitus (either on insulin therapy or using oral hypoglycemic agents), hypertension, alcoholism, overt thyroid disease, or cardiovascular diseases were excluded from the study.

Written informed consent was taken from the subjects on the study proforma before commencing the study procedures. Complete confidentiality of all data was ensured. Clinical history, examination and laboratory tests of patients were recorded. Assessments were done for comorbidities like diabetes mellitus, hypertension and obesity, which are implicated in the pathophysiology of MI, in order to eliminate the potential skewing of the data due to confounders. Blood pressure (BP) was measured from the brachial artery using a mercury sphygmomanometer after ensuring that the subject had 10 minutes of rest. Two readings were taken 10 minutes apart and their mean was recorded. Waist circumference (WC) was measured with a standard measuring tape, at the end of normal expiration to the nearest 0.1 inch, measuring at the narrowest point between the lower ribs and the iliac crest. WC, a constant measure of abdominal obesity, was employed due to ease of measurement. Unlike the waist-hip ratio, WC avoids taking hips into account as in addition to fat, hips comprise of skeletal muscle and bone, which do not have an adverse relationship with atherosclerosis, hypertension and diabetes. Independent of body mass index (BMI), WC has a strong association with mortality risk and is one of the criteria for metabolic syndrome [12]. Blood samples were collected in the morning between 8-10 am from subjects who were fasting for at least 6 hours. Blood (5 ml) was drawn from each subject in a 5cc syringe by venipuncture following aseptic measures. Serum was separated by centrifugation, collected in serum cups and stored at -20 °C until analysis. Fasting blood glucose (FBG) was checked by enzymatic-colorimetric GOD-PAP end-point method using standard reagent (Glucose PAP SL, ELITech Clinical Systems, Sées, France) and reading was taken on the Microlab 300 (ELITech Group, Puteaux, France) semi-automated clinical chemistry analyzer. Serum levels of fT3, fT4 and TSH were measured using standard enzyme-linked immunosorbent assay (ELISA) kits (CTK Biotech, Inc., Poway, California, United States) and read on an Epoch microplate spectrophotometer (BioTek Instruments, Inc., Winooski, Vermont, United States). SCH was defined as TSH above the upper limit of normal (4 mU/L) and fT4 within the normal range (9-25 pmol/L) (Your guide to thyroid function tests. Harrogate, United Kingdom: British Thyroid Foundation; 2018. Available at: https://www.btf-thyroid. org/thyroid-function-tests).

The data were statistically analyzed using Statistical Product and Service Solutions (SPSS; formerly statistical package for social sciences) version 20 (IBM® SPSS® Statistics 20.0 for Desktop Windows, IBM Corporation, Armonk, New York, United States). The Shapiro-Wilk test was applied to assess data normality. Data were described as mean ± standard deviation (SD) for normally distributed continuous variables including fT3, fT4, TSH, FBG, diastolic and systolic blood pressure, and waist circumference. For categorical variables like the presence or absence of SCH, frequencies and percentages were given. Differences in categorical variables were evaluated by a 2x2 contingency chi-square test, while group means were compared using the independent sample t-test. A p-value of less than 0.05 was considered significant.

Results

The mean age (in years) in Group I was 43.59±7.42 years and in Group II was 42.28±8.96 years, with no difference between the groups (p=0.332). The two groups were compared for BP, FBG and waist circumference, but no difference was found since patients having hypertension, diabetes mellitus and obesity have already been excluded from the study. The systolic BP (mm Hg) in Group I was 123.80±15.22 compared to 123.33±14.8 in Group II (p=0.849). The diastolic BP (mm Hg) was 77.73±12.26

in Group I as compared to 78.13±10.23 in Group II (p=0.828). The waist circumference (in inches) was 36.6±2.94 in Group I as compared to 35.6±3.26 in Group II (p=0.47). FBG (mg/dL) in Group I was 97.17±40.17 compared to 89.06±26.36 in Group II (p=0.15). In Group I, the frequency of SCH was 12% and in Group II it was 5%. Levels of TSH (mIU/L) in Group I (2.51±1.40) and Group II (2.13±1.16) showed no difference (p >0.05). No difference was found in the levels (pmol/L) of fT3 (Group I 4.58±0.42 vs. Group II 4.51±0.67, p=0.44) and fT4 (Group I 17.16±1.06 vs. Group II 17.41±2.77, p=0.46). Table 1 summarizes the comparison of various study parameters between the two groups.

Table 1. Group comparison of study parameters, including thyroid hormone profile and clinical risk factors for MI

Parameter	Group I (n=75)	Group II (n=75)	p-value
Age (years)	43.59±7.42	42.28±8.96	0.332
Systolic BP (mm Hg)	123.80±15.22	123.33±14.8	0.849
Diastolic BP (mm Hg)	77.73±12.26	78.13±10.23	0.828
WC (inches)	36.6±2.94	35.6±3.26	0.47
FBG (mg/dL)	97.17±40.17	89.06±26.36	0.15
TSH (mIU/L)	2.51±1.40	2.13± 1.16	0.11
fT3 (pmol/L)	4.58±0.42	4.51±0.67	0.44
fT4 (pmol/L)	17.16±1.06	17.41±2.77	0.46
SCH; n (%age)	9 (12%)	4 (5%)	0.15

Discussion

MI is a longstanding global health threat with more and more younger individuals becoming its victim. It is estimated that nearly one-fifth of all deaths in Pakistan are due to MI and its complications [13]. Besides the well-known risk factors, South Asian ethnicity has been identified as a predisposing factor for developing cardiovascular diseases at a younger age [14]. SCH has also been linked to the development of cardiovascular diseases by influencing lipid metabolism [15]. This study attempted to identify the link between MI and SCH in young Pakistani males. The overall prevalence of SCH in the present study population was 8.6 %, which is similar to the prevalence reported previously [16]. The prevalence of SCH in healthy individuals observed in the present study was also consistent with the findings of Alam et al. who reported a similar prevalence of SCH in the general Pakistani population [17]. Another study reported a slightly higher prevalence of SCH in the Dera Ismail Khan region of Pakistan [18], which could be attributed to a difference in the age group, as that study population included school-going children only. In the present study, 12% of the patients with MI have SCH, which is in accordance with the prevalence reported in the Rotterdam study [19].

The association of SCH with ischemic heart disease is a matter of debate. The present study did not demonstrate any link between SCH with MI. Previously, a longitudinal study with a 20-year follow-up also did not show any increase in cardiac mortality from SCH [20]. More recently, no association has been demonstrated between unrecognized SCH and cardiovascular events or mortality [21]. In a meta-analysis by Rodondi et al., only severe SCH (TSH > 10 mIU/L) was found to be associated with cardiovascular diseases, but moderate SCH (TSH levels between 4.5-10 mIU/L) was not shown to correlate with MI [16]. No case of severe SCH was found in the present study, so the association of severe SCH with MI could not be analyzed. Contrary to the present findings, some studies have found a significant correlation between SCH and MI, possibly owing to age and gender differences between their study populations and ours, as well as their prospective design, which allowed for longitudinal assessment of cardiovascular outcomes in SCH [19, 22, 23]. Based on the current findings, the role of the treatment of mild to moderate SCH in the prevention of MI cannot be suggested. Judicious prophylactic use of thyroxine in SCH has been shown to carry potential benefit, yet unwarranted administration of the same can lead to SCH [24].

The present study explored the role of SCH in MI in young men, as the risk of MI in young Pakistani males is on the rise. Most such studies have previously been conducted on females exclusively or on mixed populations [19, 23]. To the best of our knowledge, no such study has thus far been conducted to establish the correlation of MI with SCH exclusively in males, particularly in the local context. The present study is novel as it targeted a less explored aspect of MI pathophysiology in this part of the world, where the awareness of different manifestations of thyroid abnormalities is still lacking. Being a cross-sectional study, it could not suggest a cause-effect relationship. The study population comprised of male subjects only, so gender-based differences could not be assessed. The low frequency of SCH in both groups made it difficult to comprehensively study the correlation of SCH with MI. The majority of the study population belonged to areas that are not endemic for thyroid abnormalities, particularly related to iodine deficiency [25], hence the results may not be representative of the overall Pakistani population.

Conclusion

No relationship between SCH and MI could be inferred from the study and therefore, the treatment of SCH for cardioprotective benefits cannot be suggested. Whether to treat SCH to reduce the risk of future cardiovascular events still remains a controversial matter. The association of SCH with ischemic heart disease should be studied longitudinally on a larger cohort of the Pakistani population, with the inclusion of females and having a wider age range.

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